17

CHAPTER

Updates in Antimicrobial Therapy in Sepsis and Septic Shock

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INTRODUCTION

Sepsis and septic shock remain major causes of morbidity and mortality globally. As per 2017 estimates, nearly 48.9 million cases and 11 million sepsis-related deaths occurred worldwide, amounting to approximately 20% of all global deaths.[1] If left unchecked, antimicrobial resistance (AMR) could escalate these numbers, with projections of up to 10 million deaths per annum by 2050.[2]

This chapter reviews recent updates in the antimicrobial management of sepsis and septic shock, highlighting principles of empiric therapy, therapeutic drug monitoring (TDM), diagnostics, and stewardship practices, as well as future directions toward personalized care.

REDEFINING SEPSIS: CLINICAL AND DIAGNOSTIC IMPLICATIONS

The Sepsis-3 definition by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) defines sepsis as 'life-threatening organ dysfunction caused by a dysregulated host response to infection', and septic shock as a subset with significant circulatory and metabolic abnormalities associated with higher mortality.[3]

Despite such definitional advances, sepsis remains clinically heterogeneous. In a study of 300 patients, 65% had definite or likely bacterial infections, yet 35% were culture-negative, underscoring the challenge of definitive diagnosis and the importance of clinical acumen and early empiric therapy.[4]

DEFINING TREATMENT QUALITY: APPROPRIATE, ADEQUATE, AND OPTIMAL

To refine empiric therapy, three escalating targets are proposed:

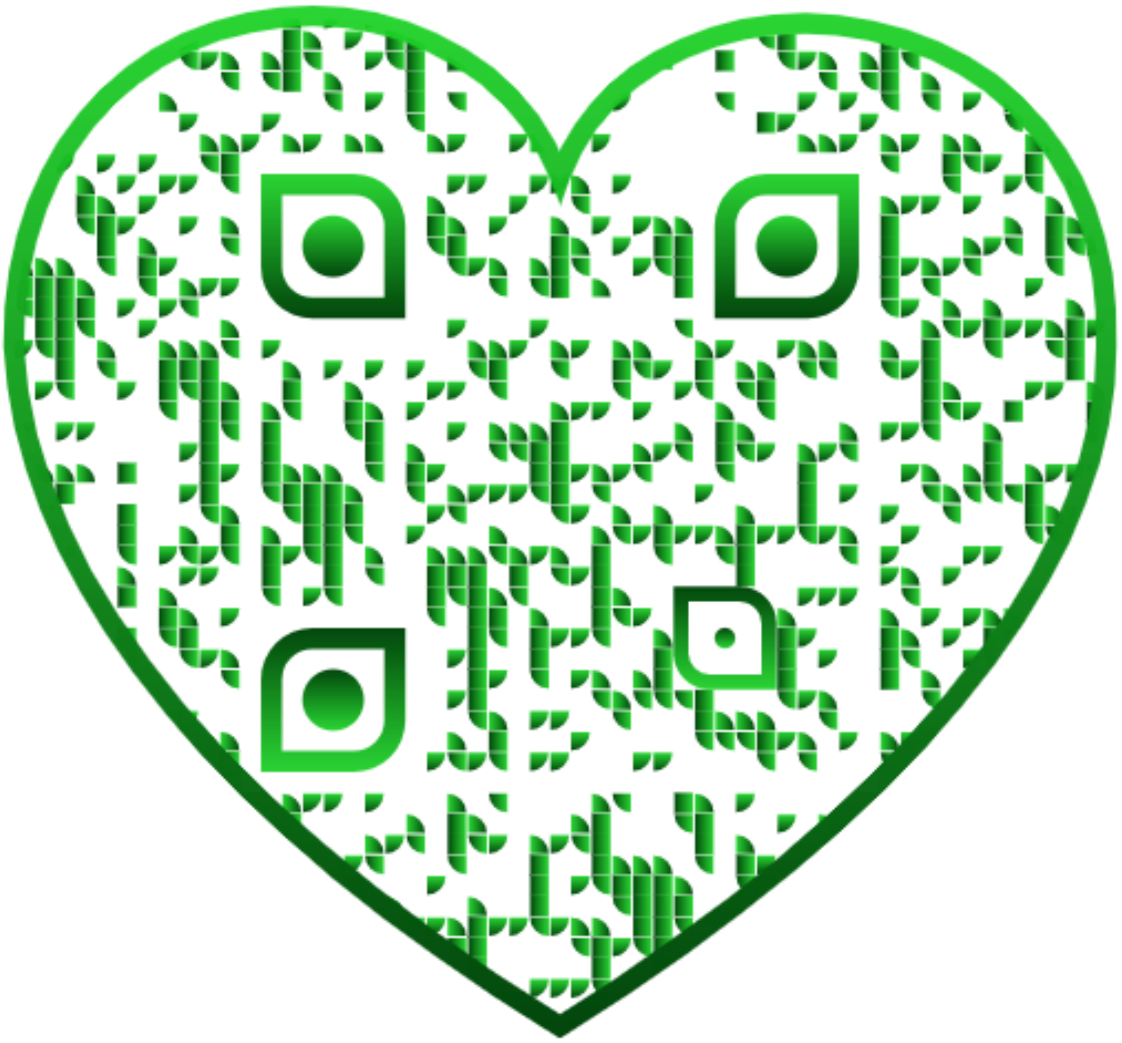
1. Appropriate therapy: Early administration of agents active against the likely pathogen(s).
2. Adequate therapy: Ensures drug concentrations reach the infected site, adjusted for pharmacokinetic (PK) and pharmacodynamic (PD) considerations.
3. Optimal therapy: Achieves effective PK/PD targets (e.g., time above MIC or AUC/MIC ratio) throughout the dosing interval. For example, β-lactams require time above MIC (T>MIC) to be maximized, favoring extended or continuous infusions in critically ill patients.

Is the Therapy Appropriate?

The success of antimicrobial therapy hinges on rapid, individualized decision-making that balances early appropriate coverage with minimizing resistance development. Choosing the right antimicrobial agent in sepsis is not a one-size-fits-all decision but rather an evolving process, informed by microbiological, clinical, and pharmacological factors. Empiric broad-spectrum antibiotic therapy is central to the initial management of severe sepsis and septic shock.

Prompt and Appropriate Empiric Therapy

Early antibiotic administration is critical to survival. Mortality increases by approximately 7–9% for every hour of delay in initiating antibiotics following the onset of septic shock.[5,6] One study reported that a 166-minute median delay was



associated with a 19% 1-year mortality, with each additional hour increasing the risk by 10%.[7]

However, not all early interventions improve outcomes. In the PHANTASi trial, prehospital antibiotic administration in non-shock patients reduced the time to antibiotics but did not improve survival, highlighting the importance of additionally tailoring therapy to the illness.[8]

The Surviving Sepsis Campaign (SSC) guidelines recommend prompt administration of antimicrobials based on clinical assessment, suspected pathogens [including methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) organisms], and possible viral or fungal sources.[9] Early, broad, and targeted antimicrobial administration—guided by clinical judgment and rapid diagnostics—is a cornerstone of sepsis care and antimicrobial stewardship.

Broad-spectrum antimicrobials should be administered within 1 hour of septic shock recognition and 3 hours for sepsis without shock.[9]

Multidrug-resistant Risk-based Empiric Choice

Current guidelines emphasize using sepsis screening tools to identify likely bacterial infections quickly and initiate empirical therapy. 'Appropriate' empiric therapy means more than just timely administration. It involves using agents that are active *in vitro* against the likely pathogens and suited to the specific clinical context.

- Empiric therapy should be broad enough to cover likely pathogens and MDR organisms, guided by:
- Site of infection
- Patient-specific risk factors (e.g., prior antibiotic use, hospitalization)
- Risk factors for MDR organisms:
    - Prior colonization or infection with MDR organisms in the past year
    - Broad-spectrum antibiotic use in the previous 90 days
    - Recent hospitalization or healthcare facility stay
    - Travel to a high-endemic region
    - Local microbiological epidemiology and antibiogram data
    - Community-acquired versus hospital-acquired infection
- Local antibiogram data.

Individualized Antimicrobial Selection and De-escalation

Effective empiric therapy is guided by three interrelated domains—described by Pea and Viale.[10] As the 'antimicrobial puzzle', as follows:

1. Infection-related: Site, severity, and pathogen-role of diagnostic stewardship
    - Diagnostic stewardship and the limitations of blood cultures
        - Despite being a cornerstone of infection diagnosis, blood cultures are positive in only 28 to 49% of patients with sepsis.[11] Several factors impair cultural utility:
            - Inadequate blood volume collection
            - Prior antibiotic exposure
            - Pre-analytical delays
            - Slow laboratory turnaround
            - Contamination
        - These limitations often result in inappropriate empiric therapy and missed opportunities for de-escalation. To address these, molecular diagnostics such as PCR, NAAT, and BioFire FilmArray panels (for meningitis, pneumonia, and bloodstream infections) are being increasingly utilized. These technologies allow rapid identification of pathogens and resistance markers (e.g., NDM, OXA), facilitating more targeted therapy
        - De-escalation should follow once culture or clinical data allow. Tools like MRSA nasal swabs—given their high negative predictive value—can safely reduce unnecessary anti-MRSA coverage.
2. Drug properties: Pharmacokinetics and pharmacodynamics characteristics, and resistance risk
    - Critically ill patients often have altered drug distribution and clearance, making individualized dosing and early reassessment essential.
3. Patient characteristics: Organ dysfunction, immune status, and comorbidities.

Special Scenarios in Sepsis in the Critically Ill Guidelines for Managing Resistant Infections

Carbapenem-resistant Enterobacteriaceae (CRE): Infections due to CRE, such as *Acinetobacter baumannii*, are associated with high mortality. The INCREMENT-CPE score, derived from a 10-year retrospective cohort study, demonstrated that patients with a high INCREMENT score benefited from combination antimicrobial therapy.[12] In addition, this score has been shown to predict mortality in CRE bacteremia, as follows:[13]

- Score <8: 18% mortality
- Score 9–13: 50% mortality
- Score >13: 80% mortality.

The choice of antibiotics in the treatment of resistant gram-negative infections—especially extended-spectrum cephalosporin-resistant and carbapenem-resistant organisms—must be guided by the type of resistance mechanism, patient stability, and local susceptibility patterns.

A structured clinical decision-making framework is discussed below.

Cephalosporin-resistant Infections

Options based on hemodynamic status are:

- Hemodynamically unstable: Meropenem or imipenem-cilastatin
- Stable: Ertapenem.

Carbapenem-resistant Enterobacteriaceae

The choice of antibiotic therapy should be guided by the underlying carbapenemase genotype, as outlined in **table 1**.

Alternatives for any of the above carbapenemase genotype categories may include older antibiotics such as aminoglycosides, tigecycline, polymyxins, or colistin, selected based on susceptibility testing and the site of infection. Eravacycline can be considered specifically for complicated intra-abdominal infections.

Carbapenem-resistant *Acinetobacter baumannii (CR-Ab)*

The preferred approach includes:

- Combination therapy with:
  - Sulbactam-durlobactam (if available), or
  - High dose sulbactam + an *in vitro* active agent such as cefiderocol, minocycline, tigecycline, or polymyxins
- Real-world data suggest cefiderocol-based regimens may have superior outcomes in severe CR-Ab infections.

Carbapenem-resistant *Pseudomonas aeruginosa (CR-Pa)*

Treatment selection should be guided by susceptibility testing and the presence or absence of carbapenemase or metallo-β-lactamase (MBL) production:

- If susceptible: Traditional agents at optimized doses
- If resistant: Newer agents (e.g., ceftolozane-tazobactam, cefiderocol); ceftolozane-tazobactam and ceftazidime-avibactam are preferred agents when there is no carbapenemase or MBL production.

Methicillin-resistant *Staphylococcus aureus*

The risk factors include:

- Previous MRSA colonization or infection
- Chronic vascular access or hemodialysis
- Recent IV antibiotic use
- Prolonged hospitalization or nursing home stay.

In such patients, empiric coverage with vancomycin or linezolid is reasonable pending culture results.

Invasive Fungal Infections: When to Consider Antifungals?

Critically ill patients with prolonged ICU stays, mechanical ventilation, and prior broad-spectrum antibiotic exposure may develop invasive *Candida* infection. The 2016 IDSA guidelines recommend empiric antifungal therapy in high-risk patients without another clear source of fever.[14]

Table 1: Antibiotic options based on carbapenemase genotype.

Carbapenemase genotype	Preferred options
KPC-producing organisms	• Ceftazidime-avibactam • Meropenem-vaborbactam
OXA-48-producing organisms	• Ceftazidime-avibactam • Cefiderocol
Metallo-β-lactamase (e.g., NDM) producing organisms	• Aztreonam-avibactam • Ceftazidime-avibactam + aztreonam • Cefiderocol

First-line agents for patients with shock include echinocandins like:

- Caspofungin: 70 mg loading, then 50 mg daily
- Micafungin: 100 mg daily
- Anidulafungin: 200 mg loading, then 100 mg daily.

A clinical trial involving 251 ICU patients showed no significant survival benefit with empiric micafungin compared to placebo (68% vs. 60.2% infection-free survival by day 28, CI 0.87–2.08), suggesting the need for better biomarkers to guide antifungal initiation.[15]

Duration of treatment typically extends to 2 weeks from culture negativity or if clinical improvement occurs, even in culture-negative cases. In patients who remain culture-negative and asymptomatic after 4–5 days, antifungal therapy may be safely discontinued.

Is the Therapy Adequate and Optimal?

Adequate therapy ensures that drug concentrations at the site of infection are sufficient and adjusted for PK and PD considerations.

Optimal therapy goes a step further by achieving effective PK/PD targets—such as maintaining drug levels above the minimum inhibitory concentration (MIC) or achieving the desired area under the curve to MIC (AUC/MIC) ratio—throughout the dosing interval.

Antibiotic Dosing in the Critically Ill: PK/PD Principles

Effective antimicrobial therapy in critically ill patients requires careful attention to PK and PD principles. Profound physiological changes—such as altered volume of distribution, protein binding, and renal clearance—can make standard dosing inadequate and increase the risk of both underdosing and toxicity.

Altered Pharmacokinetics and the Case for Individualization

Critically ill patients frequently exhibit hypoalbuminemia, a condition that profoundly impacts the pharmacokinetics of highly protein-bound antibiotics such as β-lactams, teicoplanin, daptomycin, tigecycline, clindamycin, and erythromycin. Low serum albumin levels increase the free (active) fraction of these drugs, which can either improve efficacy or increase toxicity depending on the drug and clinical context.

Conversely, non-protein-bound agents like vancomycin, polymyxins, aminoglycosides, fluoroquinolones, and linezolid are less affected by hypoalbuminemia but still require dosing adjustments based on renal function and volume status.

Another key challenge is augmented renal clearance (ARC), common in younger, trauma, or post-operative ICU patients. ARC leads to increased elimination of renally cleared antibiotics—including aminoglycosides, β-lactams, glycopeptides (vancomycin and teicoplanin), polymyxins, daptomycin, linezolid, and fluoroquinolones—which could result in subtherapeutic drug levels despite standard dosing regimens.[16]

Optimizing antibiotic exposure involves aligning drug dosing with PK/PD targets:

- Time-dependent antibiotics (e.g., β-lactams): Aim for T>MIC, where plasma concentration remains above the minimum inhibitory concentration for a significant portion of the dosing interval
- Concentration-dependent antibiotics (e.g., aminoglycosides): Efficacy correlates with a high peak/MIC ratio
- AUC-dependent agents (e.g., vancomycin, fluoroquinolones): Target the AUC/MIC ratio for best outcomes.

To achieve these targets, particularly in critically ill patients with altered PK, the following strategies are recommended:

- Loading doses for rapid attainment of therapeutic concentrations—especially with hydrophilic, time-dependent drugs
- Extended or continuous infusions for β-lactams and similar agents to maximize time above MIC.

Studies show that traditional intermittent dosing frequently fails to meet PK/PD targets. In one early study involving 80 ICU patients, T>MIC was only achieved in 57% of meropenem cases, 45% of ceftazidime, 32% of cefepime, and 33% of piperacillin-tazobactam, even though all were dosed per standard regimens.[17]

Is the therapy adequate and optimal? The Role of Therapeutic Drug Monitoring

Therapeutic drug monitoring is increasingly integral to antimicrobial management in the ICU. For drugs with a narrow therapeutic index (e.g., vancomycin, aminoglycosides, polymyxins), TDM ensures that drug levels are within the therapeutic range, reducing the risk of both treatment failure and toxicity. It also allows dynamic dosing adjustments based on patient-specific PK variability—essential in unstable, critically ill populations.

The phenomenon of MIC creep—a gradual rise in MIC values over time—can indicate evolving resistance and inadequate drug exposure, and insufficient therapeutic drug levels. Failing to maintain adequate antibiotic concentrations may accelerate resistance selection, reinforcing the need for optimized dosing.

Duration of Therapy

Historically, sepsis therapy durations were 10–14 days, but recent data support shorter courses. The recent BALANCE trial among hospitalized patients (including the critically ill) with bloodstream infection, antibiotic duration for 7 days was non-inferior to treatment for 14 days.[18] Therapy should be personalized based on clinical response, biomarkers, and imaging.

Randomized controlled trials and meta-analyses have shown that using procalcitonin (PCT) levels to guide antibiotic therapy is especially effective in determining when to stop treatment. This strategy has been associated with reduced antibiotic use, shorter hospital stays, and lower healthcare costs.[19]

REAL-WORLD GAPS ON ANTIBIOTIC APPROPRIATENESS

In a retrospective review of over 32,000 adult patients with bloodstream infections, *Escherichia coli* accounted for 58.4% and *Staphylococcus aureus* for 31.8%.[20] Inappropriate empiric coverage occurred in close to half of MRSA and CRE cases.

This reflects the ongoing need for improved stewardship and early identification of resistant organisms.

ANTIMICROBIAL STEWARDSHIP

Key pillars from the multidisciplinary statement on antimicrobial stewardship (AMS) in the ICU by Cortegiani et al.[21] It highlights a structured framework to optimize antimicrobial use while minimizing resistance. Core components include:

- Specific rationale and aims: Emphasizing patient safety, outcome improvement, and resistance mitigation
- Surveillance: Continuous monitoring of local epidemiology and resistance trends
- PK/PD principles and targets: Dosing antimicrobials based on pharmacokinetic/pharmacodynamic parameters for critically ill patients
- Therapeutic drug monitoring: Measuring drug levels to ensure efficacy while avoiding toxicity
- Fast microbiology: Incorporation of rapid diagnostic tools for timely and targeted therapy

- Quasi-targeted therapy: Empirical therapy refined using local epidemiological data.

These elements reflect a shift from broad empirical use to individualized, evidence-based strategies, requiring collaboration between intensivists, infectious disease specialists, pharmacists, and microbiologists.

THE FUTURE

The way forward in sepsis management requires a multifaceted approach that emphasizes personalized therapy through precision medicine, ensuring treatment is tailored to each patient's specific needs. A critical first step is the early and accurate identification of sepsis—an area where the role of molecular diagnostics must be further strengthened. Recognizing the stage of sepsis is essential to guide timely and appropriate interventions. Selecting the right antimicrobial agent, including the use of new or emerging drugs, is crucial in the context of rising antimicrobial resistance. Equally important is ensuring the correct dosage through therapeutic drug monitoring, which helps maximize efficacy while minimizing toxicity.

CONCLUSION

In critically ill patients, antimicrobial therapy is a dynamic, evolving process that must consider profound physiological changes, real-time drug levels, and pathogen profiles. Relying on standard dosing can lead to both therapeutic failure and resistance development. Instead, clinicians must adopt individualized strategies incorporating PK/PD optimization, TDM, early therapy, and rapid diagnostics. These principles not only improve outcomes but also form the bedrock of antimicrobial stewardship in the ICU.

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